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FIVE-MEMBERED HETEROCYCLIC ACID AMIDE ANALOG
[Goin fukuso kan san amido rui]

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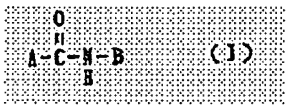
TITLE (54): FIVE-MEMBERED HETEROCYCLIC ACID AMIDE ANALOG

FOREIGN TITLE [54A]: GOIN FUKUSO KAN SAN AMIDO RUI

[Claims] /*

[Claim 1] A five-membered heterocyclic acid amide analog or its salt as shown by the general formula (I) below:

[Chemical structure 1]



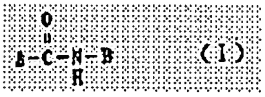
(wherein in the above formula, A is a five-membered heterocyclic group which may have a substituent group and B is an azabicycloalkyl group which may have a substituent group).

[Claim 2] The five-membered heterocyclic acid amide analog or its salt as described in Claim 1, wherein A is a pyrazolyl group which may have a substituent group.

[Claim 3] The five-membered heterocyclic acid amide analog or its salt as described in Claim 2, wherein B is 9-azabicyclo[3.3.1]nonyl group.

[Claim 4] A method of manufacturing a five-membered heterocyclic acid amide analog or its salt as shown by the general formula (I) below:

[Chemical structure 2]



(wherein in the above formula, A and B have the same meanings as above), characterized in that said compound is manufactured by the condensation reaction of a compound as shown by the general formula below:

A-CO-X

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*Claim and paragraph numbers correspond to those in the foreign text.

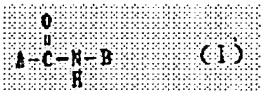
(wherein in the above formula, A is a five-membered heterocyclic group which may have a substituent group and X is hydroxyl or its reactive derivative) and a compound as shown by the general formula below:

$B\text{-}NH_2$

(wherein in the above formula, B is an azabicycloalkyl group which may have a substituent group).

[Claim 5] A serotonin antagonist having a five-membered heterocyclic acid amide analog or its pharmaceutically acceptable salt having a general formula as shown by the general formula (I):

[Chemical structure 3]

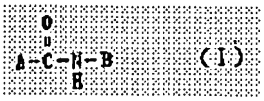


(I)

(wherein in the above formula, A is a five-membered heterocyclic group which may have a substituent group and B is an azabicycloalkyl group which may have a substituent group) as an active component.

[Claim 6] A gastrointestinal tract function regulator having a five-membered heterocyclic acid amide analog or its pharmaceutically acceptable salt having a general formula as shown by the general formula (I):

[Chemical structure 4]

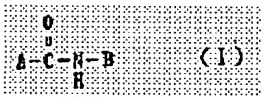


(I)

(wherein in the above formula, A is a five-membered heterocyclic group which may have a substituent group and B is an azabicycloalkyl group) as an active component.

[Claim 7] A senile dementia-preventive or therapeutic agent having a five-membered heterocyclic acid amide analog or its pharmaceutically acceptable salt having a general formula as shown by the general formula (I):

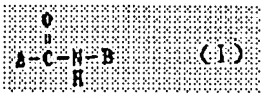
[Chemical structure 5]



(wherein in the above formula, A is a five-membered heterocyclic group which may have a substituent group and B is an azabicycloalkyl group) as an active component.

[Claim 8] A vomiting-preventive or therapeutic agent having a five-membered heterocyclic acid amide analog or its pharmaceutically acceptable salt having a general formula as shown by the general formula (I):

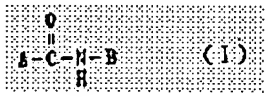
[Chemical structure 6]



(wherein in the above formula, A is a five-membered heterocyclic group which may have a substituent group and B is an azabicycloalkyl group) as an active component.

[Claim 9] An Alzheimer's type senile dementia-preventive or therapeutic agent having a five-membered heterocyclic acid amide analog or its pharmaceutically acceptable salt having a general formula as shown by the general formula (I):

[Chemical structure 7]



(wherein in the above formula, A is a five-membered heterocyclic group which may have a substituent group and B is an azabicycloalkyl group) as an active component.

[Detailed explanation of the invention]

[0001] [Industrial application area]

The present invention relates to a novel five-membered heterocyclic acid amide analog or its salt, which is useful as a drug, in particular, for prevention and therapy of diseases related to gastrointestinal tract dysfunction.

[0002] [Prior arts and the problem to be solved by the invention]

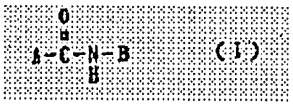
Currently, for therapy or prevention of a disease related to gastrointestinal tract dysfunction, dopamine antagonists have been mainly used as a gastrointestinal function enhancer (for example, JP-A (Tokkai) Sho52-83679, Sho60-123485). However, the above dopamine antagonists exhibit a side effect which affects the extrapyramidal system and their use have been subjected to various restrictions. Also, for the treatment of migraine headache and vomiting, several types of polycyclic heterocyclic

compounds have been known as a 5-hydroxyltryptamine (serotonin) antagonist (for example, JP-A (Tokugan) Sho62-77380, Sho61-210083). However, it has not been able to develop a completely satisfactory serotonin antagonist in terms of the effectiveness and prevention of the side effects. Under the above background, the present invention provides a five-membered heterocyclic acid amide analog or its salt which exhibits excellent therapeutic or preventive effect for diseases related to gastrointestinal tract dysfunction without exhibiting a side effect which affects the extrapyramidal system.

[0003] [Means to solve the problem]

The present inventors have done extensive research to find a compound which is effective for a disease related to gastrointestinal tract dysfunction, particularly for prevention or therapy of vomiting and nausea, and found that a five-membered heterocyclic acid amide analog having a general formula as shown below:

[Chemical structure 8]



(wherein in the above formula, A is a five-membered heterocyclic group which may have a substituent group; and B is an azabicycloalkyl group which may have a substituent group) (hereinafter, sometimes simply referred to as "the compound I") or its salt, which the present inventors successfully synthesized, exhibits excellent antiemetic effect. After further

investigation, the present inventors have successfully completed the present invention.

[0004] That is, the present invention provides a five-membered heterocyclic acid amide analog or its salt as shown by the general formula (I). Also, the present invention provides a gastrointestinal function regulator, an antiemetic agent, and a therapeutic and preventive agent for several types of senile dementia and Alzheimer's type senile dementia which have the compound (I) or its pharmaceutically acceptable salt as an active component.

[0005] The "five-membered heterocyclic group", which is represented as A in the above general formula (I), means a saturated or unsaturated heterocyclic group containing 1 ~ 4 nitrogen, oxygen, or sulfur atom. As examples of such group, an unsaturated five-membered heterocyclic group such as pyrazolyl, imidazolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, furazanyl, pyrolyl, thienyl, furyl, tetrazolyl and the like, a saturated or non-conjugated unsaturated five-membered heterocyclic group such as pyrazolidinyl, pyrazolynyl, pyrolynyl, pyrolidinyl, imidazolidinyl, imidazolinyl, thiazolidinyl and the like, can be mentioned. As particularly preferable groups, unsaturated five-membered heterocyclic groups such as pyrazolyl, isooxazolyl, pyrolyl, imidazolyl and the like, can be mentioned.

[0006] The five-membered heterocyclic group which is represented as A in the above general formula (I) may have a substituent group on the carbon atom or the nitrogen atom which constitutes the five-membered ring

at the same time or separately. As examples of such a substituent group, an alkyl group with carbon numbers of 1 ~ 6 (for example, methyl, ethyl, propyl, isopropyl, butyl, hexyl, 4-methylpentyl), an alkenyl group with carbon numbers of 2 ~4, such as vinyl, aryl [sic. : Translator's comment: should be eliminated], 2-butenyl and the like, an alkynyl group with carbon numbers of 2 ~4 such as propargyl, 2-butynyl and the like, an aryl group such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, benzothiazolyl, quinolyl, pyridyl, phthalazinyl and the like which may have a substituent group, an aralkyl group such as phenylmethyl, phenylethyl, phenylpropyl, phenylbutyl, diphenylmethyl, naphthylmethyl, naphthylethyl and the like which may have a substituent group, a nitrogen-containing heterocyclic alkyl group such as pyridylmethyl, naphthyridinylmethyl, indolylmethyl and the like which may have a substituent group, and the like, can be mentioned.

[0007] The aryl group, the aralkyl group, or the nitrogen-containing heterocyclic alkyl group may contain 1 ~ 3 substituent groups on its ring. As the substituent group, for example, an alkyl group with carbon numbers of 1 ~ 4 (for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl), an alkoxy group with carbon numbers of 1 ~ 3 (for example, methoxy, ethoxy butoxy), cyano, nitro, amino, an acylamino with carbon numbers of 1 ~ 4 (for example, formylamino, acetylamino, propionylamino), a mono-or di-$C_{1\sim6}$ alkylamino, a 5 ~ 7-membered cyclic amino, a hydroxyl group, a halogen (for example, chlorine, fluorine, bromine, iodine), a perfluoro $C_{1\sim4}$ alkyl

group (for example, trifluoromethyl, trifluoroethyl, pentafluoroethyl) and the like, can be mentioned.

[0008] The five-membered heterocyclic group which is represented as A in the above general formula (I) is bonded, through the acid amide bonding, with the bicycloalkyl group which is represented as B at the carbon atom or the nitrogen atom, or preferably at the carbon atom, which constitutes the five-membered ring.

[0009] The "azabicycloalkyl group" which is represented as B in the above general formula (I) is a nitrogen-containing bridged cyclic hydrocarbon with carbon numbers of 6 ~ 10. The nitrogen atom may be at the bridgehead position or not. When it is not at the bridgehead position, it may have an alkyl substituent group with carbon numbers of 1 ~ 4. As examples of such azabicycloalkyl group, 1-azabicyclo[2.2.1]heptyl, 1-azabicyclo[2.2.2]octyl, 1-azabicyclo[3.2.1]octyl, 1-azabicyclo[3.3.1]nonyl, 1-azabicyclo[3.3.2]decyl, 8-azabicyclo[3.2.1]octyl, 8-methyl-8-azabicyclo[3.2.1]octyl, 9-azabicyclo[3.3.1]nonyl, 9-methyl-9-azabicyclo[3.3.1]nonyl and the like, can be mentioned. In particular, 1-azabicyclo[2.2.2]octyl, 8-methyl-8-azabicyclo[3.2.1]octyl, 9-methyl-9-azabicyclo[3.3.1]nonyl and the like are preferable azabicycloalkyl groups.

[0010] The azabicycloalkyl group, which is represented as B in the above general formula (I), contains an amino group on the carbon atom at a non-bridgehead position and this amino group forms an amide bonding with a carboxyl group which is present in the five-membered heterocyclic group,

which is represented as A, in the synthesis of the compound (I) of the present invention. Such amino group may be present at any non-bridgehead positions. Furthermore, the amino group may form a structure of an exo- or endo-stereoisomer, depending of the bonding position. The present invention includes both stereoisomers. In particular, the endo-stereoisomer is preferable.

[0011] The compound (I) of the present invention is synthesized by the following method. That is, it can be synthesized by condensation reaction of the compound having the general formula (II) as shown below:

A-CO-X (II)

(wherein in the above formula, A has the same meaning as above and X is hydroxyl or its reactive derivative), with a compound having a general formula (III) as shown below:

$B-NH_2$ (III)

(wherein in the above formula, B has the same meaning as above).

[0012] As the reactive derivative which is represented as X in the compound (II), a halogen (for example, fluorine, chlorine, bromine, iodine and the like, or preferably chlorine or bromine), a lower ($C_{1\sim4}$) alkoxy (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy), N-hydroxydiacylimide ester (for example, N-hydroxysuccinic imide ester, N-hydroxyphthalimide ester, N-hydroxy-5-norbornene-2,3-dicarboximide ester) and the like, can be mentioned.

[0013] The compound in which X is a halogen, that is, an acid halide, can be manufactured by halogenation of a compound in which X is hydroxyl,

that is, carboxylic acid, using conventional methods, for example, using a halogenation agent (such as phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride, phosphorus pentabromide, phosphorus trichloride, phosphorus tribromide, thionyl chloride, thionyl bromide, sulfuryl chloride, oxalyl chloride, cyanuric chloride, boron tribromide, hydrogen iodide). As the solvent to be used in the halogenation reaction, conventionally used inert solvents, for example, chloroform, dichloromethane, dichloroethane, benzene, toluene and the like, are preferably used.

[0014] The reaction of the compound (II) with the compound (III) can be carried out using conventionally known methods. For example, the compound (II: X = hydroxyl) is converted to the compound (II: X = halogen) using a conventional method, which is reacted with the compound (III). Or, the compound (II: X = hydroxyl) is directly reacted with the compound (III) in the presence of an acid activation agent such as carbonyldiimidazole, dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide and the like. Or the compound (II: X = lower alkoxy) is directly reacted with the compound (III). The above reactions are normally carried out in an organic solvent such as a hydrocarbon-type solvent (for example, pentane, hexane, benzene, toluene), a halogenated hydrocarbon solvent (for example, dichloromethane, chloroform, dichloroethane, carbon tetrachloride), an ether-type solvent (for example, ethyl ether, tetrahydrofuran, dioxane, dimethoxyethane), an ester-type solvent (for example, ethyl acetate, butyl acetate, ethyl propionate), an amide-type solvent (for example, dimethyl

formamide, dimethyl acetamide, hexamethylphosphonotriamide), dimethyl sulfoxide and the like, under a cooled condition (-10 ~ 10°C), a room temperature (11 ~ 40°C), or under a heated condition (41 ~ 120°C). The reaction time is normally in the range of 10 minutes ~ 12 hours. The amount of the compound (III) to be used is preferably in the range of 1.0 ~ 3.0 equivalent based on the compound (II). Furthermore, the above reaction may be carried out, as necessary, in the presence of an organic base such as pyridine, 4-dimethylaminopyridine, triethylamine, diisopropylamine, triethylenediamine, tetramethylethylenediamine and the like or an inorganic base such as sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide and the like.

[0015] When the reactive derivatives of the above compound (II: X = hydroxyl) are N-hydroxydiacylimide esters, the reaction of these reactive derivates with the compound (III) is normally carried out in a solvent such as dichloromethane, tetrahydrofuran, chloroform, dimethylformamide, acetonitrile, water or the like. However, the reaction can be carried out in any other solvents as long as they would not interfere with the reaction. The reaction is carried out, as necessary, in the presence of the above-mentioned organic amine-type base or inorganic base. The reaction temperature is normally in the range of -10 ~ 100°C, or preferably 0 ~ 30°C.

[0016] The compound (II) in which X is hydroxyl can be easily obtained by the hydrolysis of a compound in which X is a lower alkoxy group, that

is, an ester, using conventionally known methods, for example, using an alkali metal hydroxide (for example, sodium hydroxide, lithium hydroxide, and potassium hydroxide), an alkali metal carbonate compound (for example, potassium carbonate, sodium carbonate, lithium carbonate), a mineral acid (for example, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid), or an organic acid (for example, acetic acid, propionic acid, trifluoroacetic acid, monochloroacetic acid, trichloroacetic acid, methanesulfonic acid, toluenesulfonic acid). As the solvent to be used in the hydrolysis reaction, any solvents, which can be used in the general hydrolysis reaction, can be used. For example, water, a lower ($C_{1\sim4}$) alkanol (for example, methanol, ethanol, propanol, butanol), dioxane, dimethylformamide and the like, are preferably used. When the organic acid is to be used, a use of the solvent may not be necessary. The reaction is normally carried out at a temperature in the range of -5 ~ 120°C, or preferably 0 ~ 80°C.

[0017] The compound (II: X = lower alkoxy or hydroxyl group) can be manufactured using conventionally known methods or similar methods. For example, a pyrazole-3-carboxylic acid ester derivative can be synthesized using the same or the similar method as described in the articles of; Aust. J. Chem., Vol. 36, PP 135 ~147 (1983); J. Prakt. Chem., Vol. 143, p 259 (1953); and Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Ring, Vol. 22 (1967), edited by Arnold Weissberger. Imidazole-2-carboxylic acid derivative can be synthesized by following the same or similar method as described in the article of J. Am. Chem. Soc.,

Vol. 71, P 383, (1949). An imidazole-5-carboxylic acid derivative can be synthesized following the same or similar method as described in the article of J. Med. Chem., Vol.8, P 220 (1964).

[0018] On the other hand, azabicycloalkaneamines as shown by the compound (III) can be synthesized using the same or similar methods as described in the articles of J. Am. Chem. Soc. Vol.73, P 3416 (1951) and JP-A (Tokkai) Sho55-92384.

[0019] When the compound (I) has optical isomers, the present invention naturally includes these isomers and a racemic compound. The compound (I) of the present invention is normally obtained as a racemic compound. However, as necessary, it can be separated into optically active isomers and each optically active isomer can be isolated.

[0020] Also, the compound (I) of the present invention may be in the form of an acid addition salt, or preferably pharmaceutically acceptable acid addition salt. For example, acid addition salts with an inorganic acid (for example, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid), or an organic acid (for example, acetic acid, propionic acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid) can be mentioned.

[0021] The compound (I) of the present invention exhibits gastrointestinal function enhancement effect, antiemetic effect, and serotonin receptor antagonistic effect (especially 5-HT_3 receptor antagonistic effect) and is effective in prevention and therapy for various

diseases related to a digestive system such as indefinite complaints of the gastrointestinal tract, indigestion, abnormal gastric emptying (in particular, delayed gastric emptying), peptic ulcer and the like. Furthermore, it is effective for prevention and therapy for nausea and vomiting associated with cancer chemotherapy drugs (such as cisplatin) or induced by radiation-based cancer therapy. Also, the compound (I) of the present invention is effective in prevention and therapy for central nerve system dysfunction, such as anxiety, migraine headache, mental disorder and the like, and prevention and therapy for various memory impairments, mainly Alzheimer's type senile dementia.

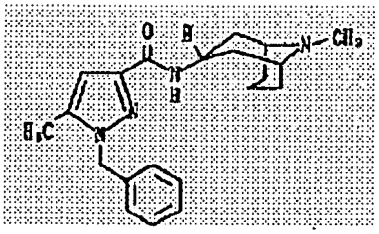
[0022] The compound (I) of the present invention is a low-toxic compound. For example, it can be safely administered to mammals including a human being orally or parenterally in a variety of forms, such as a tablet, granule capsule, injectable solution, parenteral solution, suppository and the like. Although the dose varies depending on the type of diseases, symptom and the like, it is generally, for an adult, around 0.1 ~ 100 mg per day, or preferably around 0.5 ~ 20 mg in case of oral administration. In case of parenteral administration (injectable solution), it is 0.01 ~ 10 mg per day, or preferably 0.1 ~ 5 mg.

[0023] [Example]

The present invention will be explained concretely using the examples. However, the present invention will not be restricted to these examples.

Example 1

[Chemical structure 9]



N-(Endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-phenylmethyl-5-methylpyrazole-3-carboxamide

Method A

To a solution of 1-phenylmethyl-5-methylpyrazole-3-carboxylic acid (0.7 g) in dimethylformamide (20 ml), were added triethylamine (1.0 ml), endo-9-methyl-9-azabicyclo[3.3.1]nonane-3-amine (0.5 g), and diethyl cyanophosphate (2.1 g) in that order under the ice-cooled condition. The reaction medium was stirred for 30 minutes under the ice-cooled condition. Water was added to the reaction medium and the product was extracted with dichloromethane. The extract was washed with water and dried over anhydrous magnesium sulfate. After removing the solvent by distillation, the residue was crystallized from ether, then recrystallized from ether to obtain 0.59 g of the desired product with a melting point of 128 ~ 129°C.

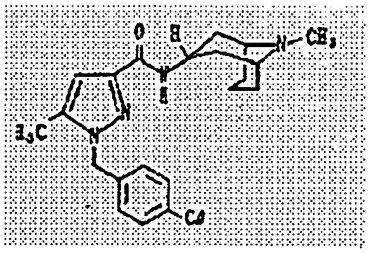
Elemental analysis for $C_{21}H_{28}N_4O$:

calculated: C 71.56; H 8.01; N 15.90

found: C 71.43; H 8.09; N 15.80

[0024] Example 2

[Chemical structure 10]



N-(Endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-(4-chlorophenyl)methyl-5-methylpyrazole-3-carboxamide

Method B

To a solution of 1-(4-chlorophenyl)methyl-5-methylpyrazole-3-carboxylic acid (1.0 g) in dichloromethane (30 ml), was added phosphorus pentachloride (2 g) in small portions under the ice-cooled condition. The mixture was stirred for 30 minutes under the ice-cooled condition. The solvent and the formed phosphorus oxychloride were removed by distillation under the reduced pressure and the residue was dissolved in dichloromethane (15 ml). To this mixture, a solution of endo-9-methyl-9-azabicyclo[3.3.1]nonane-3-amine (0.8 g) and triethylamine (1.0 ml) in dichloromethane (10 ml) was added slowly while mixing under the ice-cooled condition. The reaction medium was stirred for 1 hour at room temperature. To this reaction medium, water was added and the product was extracted with dichloromethane. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation and the obtained crude crystal was recrystallized from ether to obtain 0.91 g of the desired product with a melting point of 134 ~ 135°C.

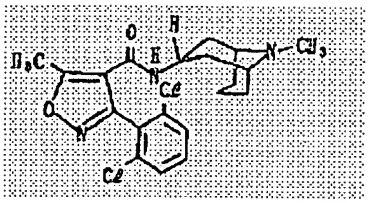
The elemental analysis for $C_{21}H_{27}ClN_4O$:

Calculated: C 65.19; H 7.03; N 14.48

found: C 65.12; H 7.05; N 14.51

[0025] Example 3

[Chemical structure 11]



N-(Endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5-methyl-3-(2,6-dichlorophenyl)isooxazole-4-carboxamide

Method C

To a solution of 5-methyl-3-(2,6-dichlorophenyl)isooxazole-4-carboxylic acid (0.6 g) in acetonitrile (10 ml), were added endo-9-methyl-9-azabicyclo[3.3.1]non-3-amine (0.5 g), N-hydroxybenztriazole (1.0 g), and dicyclohexylcarbodiimide (1.0 g) in that order while stirring under the ice-cooled condition. The reaction medium was stirred for 6 hours at a room temperature and the formed precipitated insoluble product was removed by filtration. The filtrate was concentrated under the reduced pressure to obtain an oily product. This was dissolved in dichloromethane and washed with 10% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, and water in that order. The dichloromethane solution was dried over anhydrous magnesium sulfate. When the solvent was removed by distillation, a crude crystal was obtained,

which was recrystallized from ether-ethanol (2:1) to obtain the desired product (0.49 g) with a melting point of 140 ~ 141°C.

The elemental analysis for $C_{20}H_{23}Cl_2N_3O_2$:

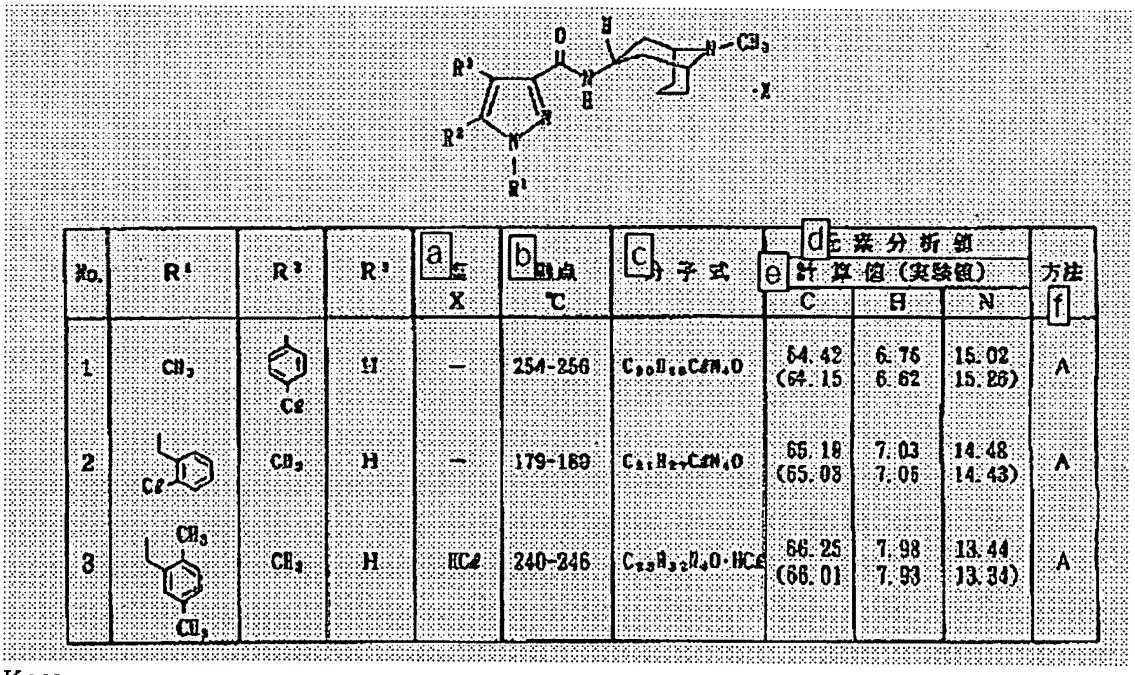
calculated: C 58.83; H 5.68; N 10.29

found: C 58.81; H 5.83; N 10.42

[0026] Example 4

Following either one of the methods A, B, and C as described in Examples 1 ~ 3, the compounds as shown in Table 1 were obtained.

[Table 1]



No.	R^1	R^2	R^3	a 盐 X	b 熔点 ℃	c 分子式	d 元素分析值 e 计算值 (实验值) C	H	N	方法 f
1	CH_3		H	—	254-256	$C_{20}H_{23}Cl_2N_3O$	64.42 (64.15	6.76 6.62	15.02 15.26)	A
2		CH_3	H	—	179-180	$C_{21}H_{25}Cl_2N_3O$	65.18 (65.08	7.03 7.06	14.48 14.43)	A
3		CH_3	H	HCl	240-246	$C_{20}H_{24}N_4O \cdot HCl$	66.25 (66.01	7.98 7.93	13.44 13.34)	A

Key:
a) Salt X
b) Melting point °C
c) Molecular formula
d) Elemental analysis
e) Calculated value (found value)
f) Method

[Table 2]

No.	R^1	R^2	R^3	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値（実験値） e C	H	N	方法 f
4		CH_3	H	—	81-83	$C_{22}H_{18}N_4O_2$	69.08 (68.88)	7.91 (8.00)	14.65 (14.62)	A
5		CH_3	H	—	122-123	$C_{21}H_{17}FN_4O$	65.08 (67.89)	7.35 (7.33)	15.12 (14.82)	A
6		CH_3	H	—	174-175	$C_{21}H_{17}N_5O_3$	63.46 (63.51)	6.85 (6.95)	17.62 (17.49)	B
7		CH_3	H	—	174-175	$C_{21}H_{17}FN_4O$	68.08 (67.98)	7.35 (7.36)	15.12 (14.90)	A
8		CH_3	H	$C_4H_4O_4$	105-109	$C_{21}H_{17}ClN_4O \cdot C_4H_4O_4$	59.70 (59.82)	6.21 (6.40)	11.14 (10.93)	A

Key:

a) Salt X

b) Melting point °C

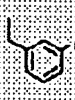
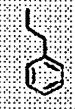
c) Molecular formula

d) Elemental analysis

e) Calculated value (found value)

f) Method

[Table 3]

No.	R¹	R²	R³	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値 (実験値) e C	H	N	方法 f
9		CH_3	H	—	141-142	$C_{21}H_{20}N_2O$	68.84 (68.63	7.95 7.94	19.06 18.85)	C
10		CH_3	H	—	195-200	$C_{21}H_{21}ClN_2O$	65.19 (65.12	7.03 7.16	14.48 14.21)	A
11		CH_3	H	—	244-246	$C_{23}H_{21}N_3O_3$	67.45 (67.29	7.63 7.60	17.10 16.83)	A
12		CH_3	H	—	155-156	$C_{23}H_{20}N_2O$	72.10 (72.00	8.25 8.31	15.20 15.13)	A
13		CH_3	H	—	80-86	$C_{21}H_{21}N_3O_3$	63.46 (63.21	6.85 6.78	17.62 17.73)	B

Key:

a) Salt X

b) Melting point °C

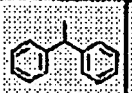
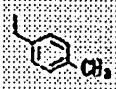
c) Molecular formula

d) Elemental analysis

e) Calculated value (found value)

f) Method

[Table 4]

No.	R^1	R^2	R^3	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 e 計算値(実験値) C	H	N	方法 f
14		CH_3	H	—	80-85	$C_{27}H_{28}N_4O$	75.67 (75.76	7.53 7.52	13.07 13.29)	A
15		CH_3	H	—	123-125	$C_{29}H_{32}N_4O$	72.10 (72.29	8.25 8.21	15.29 15.16)	A
16		C_2H_5	H	—	95-97	$C_{32}H_{34}N_4O$	72.10 (72.16	8.25 8.09	15.29 15.33)	A
17		CH_3 CH_3	H	HCl	95-98	$C_{29}H_{32}N_4O \cdot HCl$	66.26 (66.31	7.98 7.73	13.44 13.19)	A
18		CD_3	H	—	178-182	$C_{26}H_{30}N_4O$	74.59 (74.66	7.51 7.67	13.92 13.70)	A

Key:

a) Salt X

b) Melting point °C

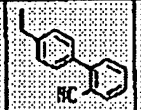
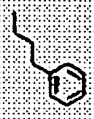
c) Molecular formula

d) Elemental analysis

e) Calculated value (found value)

f) Method

[Table 5]

No.	R¹	R²	R³	a 盐 X	b 熔点 ℃	c 分子式	d 元素分析值 计算值（实验值） C	H	N	e 方法 f
19		CH_3	H	—	135-137	$C_{16}H_{19}NO$	74.14 (74.11	6.89 6.76	15.44 15.20)	A
20			H	—	187-190	$C_{16}H_{22}ClNO$	69.55 (69.61	6.51 6.65	12.48 12.39)	B
21		CH_3	H	HCl	100-105	$C_{23}H_{23}N_4O \cdot HCl$	66.25 (66.13	7.98 8.12	13.44 13.29)	A
22		CH_3	H	—	150-151	$C_{23}H_{24}N_4O$	72.10 (71.96	8.25 8.24	15.29 15.18)	A
23		CH_3	H	—	156-158	$C_{21}H_{27}N_5O_3$	63.46 (63.55	6.85 6.95	17.62 17.51)	B

Key:

a) Salt X

b) Melting point °C

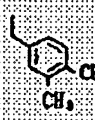
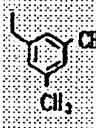
c) Molecular formula

d) Elemental analysis

e) Calculated value (found value)

f) Method

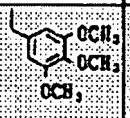
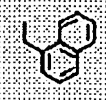
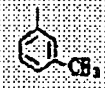
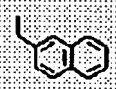
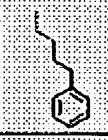
[Table 6]

No.	R^1	R^2	R^3	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値（実験値） e C	H	N	方法 f
24		CH_3	H	—	144-145	$C_{22}H_{20}N_4O$	72.10 (72.06	8.25 8.24	15.29 15.19)	A
25		CH_3	H	—	非晶状粉末 g	$C_{20}H_{22}N_4O$	72.60 (72.71	8.48 8.36	14.72 14.54)	A
26		CH_3	H	—	非晶状粉末 g	$C_{18}H_{18}N_4O$	70.97 (70.83	7.74 7.80	15.56 16.63)	A
27		CH_3	CH_3	—	128-129	$C_{23}H_{20}N_4O$	72.10 (71.97	8.25 8.26	15.29 15.20)	A
28		CH_3	H	—	174-175	$C_{22}H_{22}N_4O$	72.60 (72.48	8.48 8.61	14.72 14.73)	A

Key:

a) Salt X
b) Melting point °C
c) Molecular formula
d) Elemental analysis
e) Calculated value (found value)
f) Method
g) Noncrystalline powder

[Table 7]

No.	R¹	R²	R³	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値(実験値) e C	H	N	方法 f
29		CH_3	H	—	178-179	$C_{20}H_{24}N_4O_4$	65.14 (65.30	7.74 7.79	12.66 12.54)	A
30		C_6H_5	H	—	131-133	$C_{30}H_{32}N_4O$	74.97 (74.85	7.74 7.78	13.45 13.50)	A
31		CH_3	H	—	125-126	$C_{21}H_{28}N_4O$	71.56 (71.71	8.01 8.09	15.90 15.92)	A
32		CH_3	H	—	170-171	$C_{25}H_{30}N_4O$	74.60 (74.41	7.51 7.46	13.92 13.77)	A
33		CH_3	H	—	139-140	$C_{24}H_{32}N_4O$	73.06 (72.95	8.69 8.74	14.20 14.13)	A

Key:

a) Salt X

b) Melting point °C

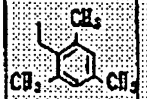
c) Molecular formula

d) Elemental analysis

e) Calculated value (found value)

f) Method

[Table 8]

No.	R^1	R^2	R^3	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 e 計算値（実験値） C	H	N	f 方法
34		CH_3	H	—	212-213	$C_{24}H_{34}N_4O$	73.06 (72.91	8.69 8.70	14.20 13.95)	A
35		CH_3	H	—	180-181	$C_{24}H_{32}N_4O$	74.20 (74.87	7.26 7.29	14.42 14.33)	A
36		CH_3	H	—	176-178	$C_{24}H_{32}N_4O$	73.43 (73.54	8.22 8.29	14.27 14.15)	A
37		CH_3	H	—	137-139	$C_{21}H_{28}N_4O$	71.56 (71.51	8.01 8.07	15.90 15.72)	A
38		CH_3	H	—	淡色状粉末 g	$C_{20}H_{25}ClN_4O \cdot HCl$	58.68 (58.49	6.40 6.29	13.69 13.41)	B

Key:

a) Salt X

b) Melting point °C

c) Molecular formula

d) Elemental analysis

e) Calculated value (found value)

f) Method

g) Noncrystalline powder

[Table 9]

No.	R^1	R^2	R^3	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値（実験値） C	H	N	e	方法 f
39		CH_3	H	2HCl	150-155	$C_{21}H_{22}N_4O \cdot 2HCl$	58.20 (59.41	7.11 7.23	13.17 13.04)		A
40		CH_3	H	HCl	非晶状粉末 g	$C_{19}H_{22}Cl_2N_4O \cdot HCl$	54.13 (53.95	5.68 5.65	12.62 12.75)		B
41		CH_3	H	—	149-151	$C_{20}H_{21}ClN_4O$	64.42 (64.38	6.76 6.87	15.02 14.81)		A
42		C_3H_5	H	—	159-161	$C_{23}H_{24}N_4O$	74.60 (74.67	7.51 7.53	13.92 13.86)		A
43		C_3H_5	H	—	147-148	$C_{21}H_{22}N_4O$	71.56 (71.47	8.01 8.22	15.90 15.87)		A

Key:

a) Salt X

b) Melting point °C

c) Molecular formula

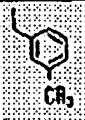
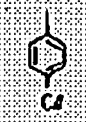
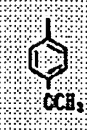
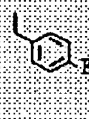
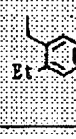
d) Elemental analysis

e) Calculated value (found value)

f) Method

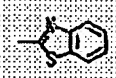
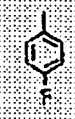
g) Noncrystalline powder

[Table 10]

No.	R^1	R^2	R^3	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値(実験値) e C	H	N	方法 f
44		C_2H_5	H	—	89-90	$C_{23}H_{32}N_4O$	72.60 (72.61	8.48 8.70	14.72 14.76)	A
45		CH_3	H	2HCℓ	160-170	$C_{20}H_{32}ClN_4O$-2HCℓ·H_2O	51.79 (51.82	6.30 6.44	12.08 12.07)	A
46		CH_3	H	HCℓ	144-148	$C_{21}H_{30}N_4O_2$·HCℓ	62.29 (62.12	7.22 7.42	13.84 13.76)	A
47		CH_3	H	—	137-139	$C_{23}H_{32}N_4O$	72.60 (72.68	8.48 8.58	14.72 14.54)	A
48		CH_3	H	—	111-113	$C_{21}H_{30}N_4O$	72.60 (72.66	8.48 8.55	14.72 14.63)	A

Key:
a) Salt X
b) Melting point °C
c) Molecular formula
d) Elemental analysis
e) Calculated value (found value)
f) Method

[Table 11]

No.	R^1	R^2	R^3	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値(実験値) e C	H	N	方法 f
49		CH_3	CH_3	—	173-176	$C_{21}H_{22}N_4O$	71.56 (71.48	8.01 7.87	15.99 15.73)	A
50		CH_3	H	—	非晶状粉末 g	$C_{19}H_{20}N_4O$	67.23 (67.61	7.42 7.56	20.63 20.77)	A
51		CH_3	H	—	199-200	$C_{21}H_{24}N_5OS$	63.77 (63.64	6.37 6.50	17.71 17.74)	C
52		CH_3	H	—	165-166	$C_{20}H_{19}FN_4O$	67.39 (67.52	7.07 7.20	15.72 15.72)	A
53		CH_3	H	—	169-171	$C_{23}H_{24}N_6O$	67.67 (67.43	6.71 6.64	21.52 21.48)	C

Key:

a) Salt X

b) Melting point °C

c) Molecular formula

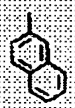
d) Elemental analysis

e) Calculated value (found value)

f) Method

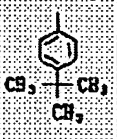
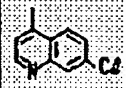
g) Noncrystalline powder

[Table 12]

No.	R^1	R^2	R^3	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値（実験値） C	H	N	e 方法 f
54		CH_3	H	—	161-162	$C_{22}H_{30}N_4O$	72.10 (72.18)	8.25 8.23	15.29 15.11)	A
55		CH_3	H	—	142-145	$C_{23}H_{32}N_4O$	72.98 (72.80)	7.99 7.97	14.80 14.75)	A
56		CH_3	H	—	147-148	$C_{24}H_{32}N_4O$	73.43 (73.57)	8.22 8.29	14.27 14.30)	A
57		CH_3	H	—	147-150	$C_{24}H_{32}N_4O$	74.20 (74.14	7.26 7.38	14.42 14.36)	A
58		CH_3	H	—	g 非晶状粉末	$C_{20}H_{23}FN_4O$	67.39 (67.47	7.07 6.82	15.72 15.54)	A

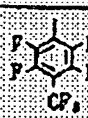
Key:
a) Salt X
b) Melting point °C
c) Molecular formula
d) Elemental analysis
e) Calculated value (found value)
f) Method
g) Noncrystalline powder

[Table 13]

No.	R^1	R^2	R^3	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値（実験値） e C	H	N	方法 f
59		CH_3	H	—	g	$C_{20}H_{26}FN_4O$	67.39 (67.27)	7.07 (7.00)	15.72 (15.63)	A
60		CH_2	H	—	g	$C_{21}H_{23}F_3N_4O$	62.06 (61.84)	6.20 (6.13)	13.78 (13.64)	A
61		CH_3	H	—	193-194	$C_{24}H_{30}N_4O$	73.06 (73.19)	8.69 (8.81)	14.20 (14.12)	A
62		CH_3	H	—	166-168	$C_{23}H_{30}N_4O$	72.10 (72.11)	8.25 (8.17)	15.29 (15.13)	A
63		CH_2	H	—	g	$C_{23}H_{29}ClN_4O$	65.16 (64.94)	6.18 (6.34)	16.52 (16.34)	C

Key:
a) Salt X
b) Melting point °C
c) Molecular formula
d) Elemental analysis
e) Calculated value (found value)
f) Method
g) Noncrystalline powder

[Table 14]

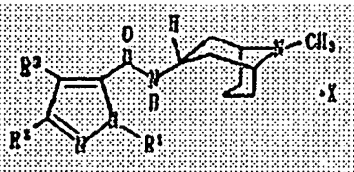
No.	R¹	R²	R³	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値（実験値） C	H	N	e 方法 f
64		CH_3	H	–	非晶状粉末 g	$C_{21}H_{21}F_7N_4O$	52.72 (52.86	4.42 4.54	11.71 11.69)	A
65		OH	H	–	185-192	$C_{19}H_{24}N_4O_3$	67.03 (67.20	7.11 7.01	16.46 16.39)	A

Key:
a) Salt X
b) Melting point °C
c) Molecular formula
d) Elemental analysis
e) Calculated value (found value)
f) Method
g) Noncrystalline powder

[0027] Example 5

Following the method A as described in Example 1, the compounds as shown in Table 2 were obtained.

[Table 15]



No.	R^1	R^2	R^3	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値（実験値） e C	H	N
1	CH_3		H	−	135-137	$C_{16}H_{15}ClN_4O$	64.42 (64.61	6.76 6.72	15.02 15.08)
2		CH_3	H	−	193-194	$C_{21}H_{18}N_4O$	71.56 (71.63	8.01 7.90	15.90 15.77)
3			H	−	非晶状粉末 f	$C_{26}H_{19}ClN_4O$	69.55 (69.68	6.51 6.48	12.48 12.33)

Key:

a) Salt X

b) Melting point °C

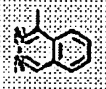
c) Molecular formula

d) Elemental analysis

e) Calculated value (found value)

f) Noncrystalline powder

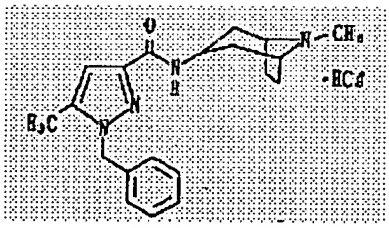
[Table 16]

No.	R¹	R²	R³	a 塩 X	b 融点 ℃	c 分子式	d 元素分析値 計算値（実験値） e C	H	N
4		CH_3	H	–	非晶状粉末 f	$C_{20}H_{26}N_4O$	70.97 (71.07)	7.74 7.55	16.56 16.62)
5		CH_3	H	HCℓ	181-185	$C_{20}H_{26}N_4O\cdot HCℓ$	60.71 (60.77	6.97 6.80	18.63 18.53)
6		CH_3	H	–	200-203	$C_{22}H_{26}N_6O$	67.67 (67.54	6.71 6.81	21.52 21.78)

Key:
a) Salt X
b) Melting point °C
c) Molecular formula
d) Elemental analysis
e) Calculated value (found value)
f) Noncrystalline powder

[0028] Example 6

[Chemical structure 12]



N-(Endo-8-azabicyclo[3.2.1]oct-3-yl)-1-phenylmethyl-5-methylpyrazole-3-carboxamide·hydrochloride

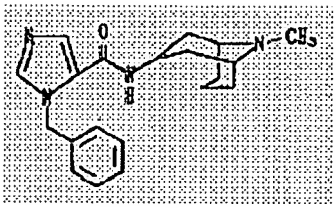
Following the method as described in Example 1, the desired product was obtained from 1-phenylmethyl-5-methylpyrazole-3-carboxylic acid and endo-8-methyl-8-azabicyclo[3.2.1]octane-3-amine. Noncrystalline powder. The elemental analysis for $C_{20}H_{26}N_4O\cdot HCl$:

calculated: C 64.07; H 7.26; N 14.94

found: C 59.98; H 7.38; N 14.85

[0029] [Example 27]

[Chemical structure 13]



N-(Endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-phenylmethylimidazole-5-carboxamide

Following the method (A) as described in Example 1, the desired product was obtained from 1-phenylmethylimidazole-5-carboxylic acid and endo-9-methyl-9-azabicyclo[3.3.1]nonane-3-amine. Melting point 181 ~182°C.

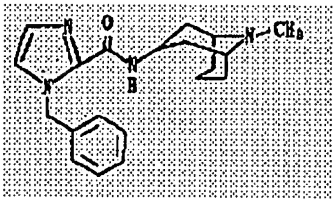
The elemental analysis for $C_{20}H_{26}N_4O$:

calculated: C 70.97; H 7.74; N 16.56

found: C 70.83; H 7.80; N 16.39

[0030] Example 8

[Chemical structure 14]



N-(Endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-phenylmethylimidazole-2-carboxamide

Following the method (A) as described in Example 1, the desired product was obtained from 1-phenylmethylimidazole-2-carboxylic acid and endo-9-methyl-9-azabicyclo[3.3.1]nonane-3-amine. Melting point 145 ~148°C.

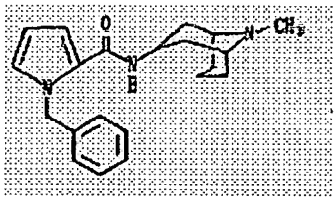
The elemental analysis for $C_{20}H_{26}N_4O$:

calculated: C 70.97; H 7.74; N 16.56

found: C 70.99; H 7.80; N 16.42

[0031] Example 9

[Chemical structure 15]



N-(Endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-phenylmethyl-pyrole-2-carboxamide

Following the method (A) as described in Example 1, the desired product was obtained from 1-phenylmethylpyrole-2-carboxylic acid and endo-9-methyl-9-azabicyclo[3.3.1]nonane-3-amine. Melting point 141 ~143°C.

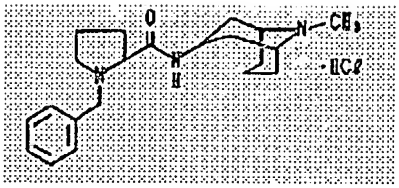
The elemental analysis for $C_{21}H_{27}N_3O$:

calculated: C 74.74; H 8.06; N 12.45

found: C 74.62; H 7.94; N 12.60

[0032] Example 10

[Chemical structure 16]



N-(Endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-phenylmethylpyrolidine-2-carboxamide·hydrochloride

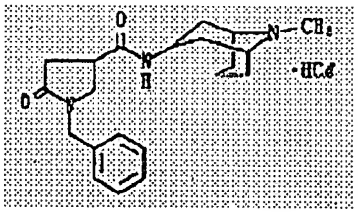
Following the method (A) as described in Example 1, the desired product was obtained from 1-phenylmethylpyrolidine-2-carboxylic acid and endo-9-methyl-9-azabicyclo[3.3.1]nonane-3-amine. Crystalline powder. The elemental analysis for $C_{21}H_{31}N_3O \cdot HCl$:

calculated: C 66.74; H 8.53; N 11.12

found: C 66.91; H 8.29; N 11.36

[0033] Example 11

[Chemical structure 17]



N-(Endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-phenylmethyl-2-pyrolidone-4-carboxamide·hydrochloride

Following the method (A) as described in Example 1, the desired product was obtained from 1-phenylmethyl-2-pyrolidone-4-carboxylic acid and endo-9-methyl-9-azabicyclo[3.3.1]nonane-3-amine. Noncrystalline powder.

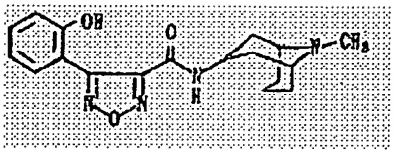
The elemental analysis for $C_{21}H_{29}N_3O_2 \cdot HCl$:

calculated: C 64.35; H 7.71; N 10.72

found: C 64.17; H 7.63; N 10.83

[0034] Example 12

[Chemical structure 18]



N-(Endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-4-(2-hydroxyphenyl)-furazane-3-carboxamide

Following the method (A) as described in Example 1, the desired product was obtained from 4-(2-hydroxyphenyl)furazane-3-carboxylic acid and endo-9-methyl-9-azabicyclo[3.3.1]nonane-3-amine. Noncrystalline powder.

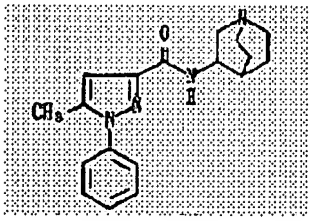
The elemental analysis for $C_{18}H_{22}N_4O_3$:

calculated: C 63.14; H 6.48; N 16.36

found: C 62.99; H 6.51; N 16.40

[0035] Example 13

[Chemical structure 19]



N-(Quinuclidine-3-yl)-5-methyl-1-phenylpyrazole-3-carboxamide

Following the method (A) as described in Example 1, the desired product was obtained from 5-methyl-1-phenylpyrazole-3-carboxylic acid and 3-aminoquinuclidine. Melting point 165 ~ 167°C.

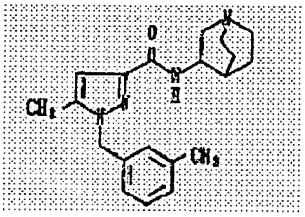
The elemental analysis for $C_{18}H_{22}N_4O$:

calculated: C 69.65; H 7.14; N 18.05

found: C 69.48; H 7.03; N 17.83

[0036] Example 14

[Chemical structure 20]



N-(Quinuclidine-3-yl)-5-methyl-1-(3-methylphenyl)methylpyrazole-3-carboxamide

Following the method (A) as described in Example 1, the desired product was obtained from 5-methyl-1-(3-methylphenyl)methylpyrazole-3-carboxylic acid and 3-aminoquinuclidine. Melting point 88 ~ 90°C.

The elemental analysis for $C_{20}H_{26}N_4O$:

calculated: C 70.97; H 7.74; N 16.56

found: C 70.82; H 7.90; N 16.48

[0037] Biological Experiment 1

<u>Suppression of contraction reaction of the ileum longitudinal muscle in guinea pig induced by serotonin (5-hydroxytryptamine; 5-HT)</u>

A guinea pig (Hartley-type, white male) was killed by a blow to the occipital region and exsanguination and its ileum was excised. A longitudinal muscle was meticulously removed from the ileum and cut to a length of around 15 mm. The prepared longitudinal muscle specimen was set in an organ bath filled with a nutrient fluid and a load of 500 mg was applied to the specimen. As the nutrient solution, a Tyrode's solution which was mixed with 0.03 mM of glycol ether diamine tetraacetate, 0.12 mM of ascorbic acid, 20 μM of choline chloride and 0.1 μM of ketanserin was used. An oxygen (O_2) - carbon dioxide (CO_2) gas mixture (97:3) was passed through the above nutrient solution while maintaining a temperature of the solution at 37°C. The contraction of the specimen was measured using an isotonic transducer. A 5-HT solution with a final concentration of 10^{-5} M was added to the organ bath to excite the specimen. After washing and 30 minutes of resting, the species was again excited by the 10^{-5}M of 5-HT solution. The above operation was repeated and when the contraction became stabilized, this contraction value was defined as the control contraction and set as 100% contraction. Subsequently, a compound to be tested was added to the organ bath in a specified concentration. Five minutes after the addition, the sample was excited again by 10^{-5} M of 5-HT. From the extent of the contraction, the degree of the contraction suppression as compared to the control contraction was obtained.

[0038] Biological Experiment 2

<u>Suppression of positive chronotropic action of the right atrium of guinea pig induced by 5-HT</u>

Immediately after smashing of a guinea pig (Hartley-type; white male) on the occipital region and thoracotomy, the heart was excised. The right atrium specimen was set in an organ bath and a load of 500 mg was applied to the specimen. As the nutrient solution, a Krebs-Hensereit solution which was mixed with 10^{-7} M of atropine was used. An oxygen (O_2) - carbon dioxide (CO_2) gas mixture (97:3) was passed through the above nutrient solution while maintaining a temperature of the solution at 37°C. The contraction of the specimen was measured using an isometric transducer. The beating rate was measured by using a tachometer. When the beating rate became stabilized, 5-HT with final concentrations of 3×10^{-7}, 10^{-6}, 3×10^{-6}, 10^{-5}, 3×10^{-5}, and 10^{-4} M were cumulatively added into an organ bath to excite the specimen. The reaction of the specimen during the above operations was defined as the control reaction. After washing, the specimen was put to rest for more than 30 minutes. When the beating rate became stabilized, the test compound was added into the organ bath. Five minutes later, the specimen was excited again with 5-HT. The positive chronotropic action of the right atrium specimen was expressed based on the maximum control reaction which was set as 100%. And the pharmaceutical effect was expressed as the degree of suppression by comparing the control reaction and the reaction in the presence of the test compound at a 5-HT concentration of 10^{-6} M.

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[0039] Biological Experiment 3

Suppression of bradycardic reaction (Bezold-Jarisch reflex) induced by intravenous administration of serotonin (5-HT)

An urethane-anaesthetized (1.4g/kg intraperitoneal administration) male Jcl:SD rat (7 ~ 9 weeks old) was used. To measure the heart rate, a polyethylene cannula (PE-50) was inserted into the left carotid artery and it was connected to a pressure transducer (MPV-0.5-290-0-III, from Nihon Kohden Co.). The obtained output was entered into a tachometer (Heart rate meter, type 2140, from San-ei Sokki Co.) to measure the heart rate. Through the polyethylene cannnula (PE-50) which was inserted into the left carotid artery, 5-HT at a dose of 100 μg/kg was administered intravenously (i.v.). The drug was dissolved in a physiological saline solution or DMSO and was administered through the tail vein at a dose of 0.1 ml/100 g. Evaluation of 5-HT_3 receptor antagonist was carried out as follows. Firstly, the bradycardic reaction induced by 5-HT at a dose of 100 μg/kg through i.v. was defined as the reaction before drug administration. After the recovery from the reaction (within 5 minutes), the drug was administered through i.v., then, after 8 ~ 10 minutes later, the same dose of 5-HT was administered through i.v. The bradycardic reaction under the above condition was defined as the reaction after the drug administration. Then, the degree of suppression was calculated according to the following formula:

% degree of suppression = [(the heart rate before drug administration - the heart rate after drug administration)/(the heart rate before drug administration)] x 100.

For each drug, the dose-response curve was constructed and this curve was expressed by the linear regression equation using the least squares method and the significance of the regression was tested. From the regression

equation, the dose required for 50% suppression (ID 50) and its 95% confidence limit was obtained.

[0040] Biological Example 4

Suppression of cisplatin-induced vomiting

To a ferret (male or female), the test compound was administered intravenously (i.v.). Immediately after administration, 10 mg/kg of cisplatin was administered intravenously. Furthermore, after 1 hour, as necessary, the test compound was administered intravenously (i.v.). Immediately after the administration of cisplatin, the number of vomiting and retching of the ferret was counted over a 3 hour-period.

The results of the Biological Examples 1 ~3 are shown in Table 3, while the results of the Biological Example 4 are shown in Table 4.

[0041] [Table 3]

The suppression of; (A)the contraction of ileum longitudinal muscle of guinea pig; (B)positive chronotropic action of the right atrium of guinea pig; and (C) bradycardic reaction (B.J. reflex) of rat.

テスト化合物 実施例番号 [a]	A、B、Cの抑制作用 [b]		
	A テスト化合物 10^{-7}M の抑制率(%)	B 同左 (%)	C ID_{50} (μg/kg, i.v.)
4-18	20.8±2.4	44.2±7.9	8.8
4-26	60.2±1.8	68.2±5.8	7.0
4-31	47.6±1.3	62.4±8.1	6.9
4-35	12.0±6.0	31.8±1.5	7.5
4-39	54.9±3.4	86.5±4.5	9.2
4-46	20.2±8.1	−	6.8
4-49	−	−	8.6
4-59	27.8±9.7	−	7.8
4-63	−	−	4.3
4-2	30.0±8.2	61.5±9.7	−

Key:
a) The test compound/Example number.
b) Suppression of A, B, and C.
A- Degree of suppression by the test compound (10^{-7}M) (%).
B- Same as the left (%).

[0042] [Table 4]
Suppression of cisplatin-induced vomiting.

[a] テスト化合物 実施例番号	[b] 投与量 μg/kg(i.v.) (1時間後追加投与の量:μg/kg, i.v.)	[c] 使用動物数 N	嘔吐(痙攣)の回数 [d]
[e] コントロール	−	9	9.4±1.1
			(72.0±13.0)
4−18	100	2	3.5±1.5
	(100)		(12.5±7.5)
4−26	300	4	5.0±2.4
			(39.3±14.4)
	100	3	1.0±1.0
	(100)		(17.0±17.0)
4−31	100	1	8
	(100)		(23)
4−35	100	2	2
			(24±2)
	100	2	0
	(100)		(0)
4−46	100	2	4.5±0.5
	(100)		(31±7)
4−53	300	2	5.5±1.5
			(53±41)

Key:
a) Test compound/Example number.
b) Dose, μg/kg (i.v.) (additional dose after 1 hour: μg/kg, i.v.).
c) The number of used animals.
d) The number of vomiting (retching).
e) Control.

[0043] Pharmaceutical preparation Example 1

(1) N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-(1-naphthyl)-5-methylpyrazole-3-carboxamide (the compound in Example 4-35) 5 g
(2) Lactose 238 g
(3) Corn starch powder 55 g
(4) Magnesium stearate 2 g

Compounds (1), (2) and 30 g of corn starch powder were mixed and this mixture was granulated together with a paste of 20 g of corn starch powder and 20 ml of water. The obtained granules were mixed with 15 g of corn starch powder

and the compound (4) and compressed to form 1,000 tablets with a diameter of 4 mm, each tablet containing 5 mg of the compound (1).

[0044] Pharmaceutical preparation 2

A mixture of 2 g of N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-(1-naphthyl)-5-methylpyrazole-3-carboxamide and 5.25 g of mannitol was dissolved in distilled water for injection. After adjusting the pH of the solution to 5 ~ 7 using 0.1% HCl, the solution was diluted with the distilled water for injection to a total volume of 1,000 ml. This solution was subjected to filter sterilization using a 0.2-μm filter and pipetted into 1,000 ampoules with a size of 1 ml.

[0045] [Effect of the invention]

As shown in the above Examples, the novel five-membered heterocyclic acid amide analog and its salt of the present invention exhibited a strong suppression effect against contraction of the gastrointestinal tract, bradycardic reaction and vomiting in guinea pig, rat and ferret. Therefore, the novel five-membered heterocyclic acid amide analog and its salt of the present invention is useful as a drug for various diseases related to a digestive system, for example, indefinite complaints of gastrointestinal tract, indigestion, delayed gastric emptying, peptic ulcer and the like. Also, it is extremely effective for prevention and therapy against vomiting and nausea induced by cancer chemotherapy drugs or radiation treatment. Furthermore, it can be used as a drug for prevention and therapy of the central nerve system disorder such as anxiety, mental disorder, migraine headache and the like and for prevention and therapy of various memory

impairments, mainly Alzheimer's type senile dementia. Therefore, the present invention provides useful drugs such as: a gastrointestinal function regulator; an antiemetic drug; a drug for central nerve system; a memory dysfunction improver; and a drug for migraine headache.